

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	
International application No. PCT/US00/03878	Applicant's or agent's file reference RU-0080
International filing date (day/month/year) 15 February 2000 (15.02.00)	Priority date (day/month/year) 16 February 1999 (16.02.99)
Applicant YURKOW, Edward, J. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 08 September 2000 (08.09.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer R. Forax Telephone No.: (41-22) 338.83.38
---	--

BEST AVAILABLE COPY

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICE OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NEW JERSEY 08053

Docket System ☒State ☒Docket BOOK ☒

8/9/01

PCT

JUL 11 2001

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing
(day/month/year)

09 JUL 2001

Applicant's or agent's file reference

RU-0080

REPLY DUE

within ONE months
from the above date of mailing

International application No.

PCT/US00/03878

International filing date (day/month/year)

15 FEBRUARY 2000

Priority date (day/month/year)

16 FEBRUARY 1999

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 39/395 and US Cl.: 424/130.1

Applicant

RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16 JUNE 2001

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MINN-TAM DAVIS

Telephone No. (703) 308-0916

WRITTEN OPINION

International application No.

PCT/US00/03878

I. Basis of the opinion

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-18 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 19 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

WRITTEN OPINION

International application No.

PCT/US00/03878

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>2-4</u>	YES
	Claims <u>1, 5</u>	NO
Inventive Step (IS)	Claims <u>2-4</u>	YES
	Claims <u>1, 5</u>	NO
Industrial Applicability (IA)	Claims <u>1-5</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations

Claims 1, 5 lack novelty under PCT Article 33(2) as being anticipated by Neal et al.

Claims 1 and 5 are drawn to a method comprising contacting cells with a redox clamping agent which maintains the cells in a selected redox state. The specification discloses that meso-2,3- dimercaptosuccinic acid is a redox clamping agent (p.6). Neal et al teach administration of 2,3-dimercaptosuccinic acid to a rat previously exposed to lead, and investigate the effects of 2,3-dimercaptosuccinic acid on the redox status of the lenses of the rat. Neal et al teach that 2,3-dimercaptosuccinic acid decreases protein bound glutathione and enhances the reductive status of lenses.

Claims 1, 5 lack an inventive step under PCT Article 33(3) as being obvious over Neal et al for the same reasons set forth.

Claims 2-4 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a method of sensitizing selected cells to a chemotherapeutic agent, or a method of treating cancer comprising contacting cells, or administering a redox clamping agent alone, or in combination with a chemotherapeutic agent.

----- NEW CITATIONS -----

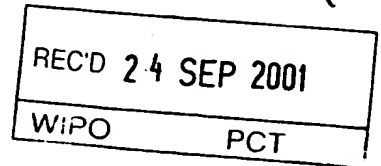
NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference RU-0080	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/116)	
International application No. PCT/US00/03878	International filing date (day/month/year) 15 FEBRUARY 2000	Priority date (day/month/year) 16 FEBRUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/395 and US Cl.: 424/150.1		
Applicant RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

I ☒ Basis of the report

II ☐ Priority

III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

Date of submission of the demand 08 SEPTEMBER 2000	Date of completion of this report 06 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer <i>Joseph Bridges for</i> VINH TAM DAVIS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0916

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/03878

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-18 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the claims:

pages 19 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the drawings:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

☒ the sequence listing part of the description:

pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/03878

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>2-4</u>	YES
	Claims <u>1, 5</u>	NO
Inventive Step (IS)	Claims <u>2-4</u>	YES
	Claims <u>1, 5</u>	NO
Industrial Applicability (IA)	Claims <u>1-5</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1, 5 lack novelty under PCT Article 33(2) as being anticipated by Neal et al.

Claims 1 and 5 are drawn to a method comprising contacting cells with a redox clamping agent which maintains the cells in a selected redox state. The specification discloses that meso-2,3- dimercaptosuccinic acid is a redox clamping agent (p.6). Neal et al teach administration of 2,3-dimercaptosuccinic acid to a rat previously exposed to lead, and investigate the effects of 2,3-dimercaptosuccinic acid on the redox status of the lenses of the rat. Neal et al teach that 2,3-dimercaptosuccinic acid decreases protein bound glutathione and enhances the reductive status of lenses.

Claims 1, 5 lack an inventive step under PCT Article 33(3) as being obvious over Neal et al for the same reasons set forth.

Claims 2-4 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest a method of sensitizing selected cells to a chemotherapeutic agent, or a method of treating cancer comprising contacting cells, or administering a redox clamping agent alone, or in combination with a chemotherapeutic agent.

----- NEW CITATIONS -----

NONE

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 39/395	A1	(11) International Publication Number: WO 00/48632 (43) International Publication Date: 24 August 2000 (24.08.00)
(21) International Application Number: PCT/US00/03878 (22) International Filing Date: 15 February 2000 (15.02.00) (30) Priority Data: 60/120,128 16 February 1999 (16.02.99) US (71) Applicant (for all designated States except US): RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; ASB, Annex 11, 58 Bevier Road, Piscataway, NJ 08854-8010 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): YURKOW, Edward, J. [US/US]; 8 Skyview Terrace, Clifton, NJ 07013 (US). MERMELSTEIN, Fred, H. [US/US]; 123 Woods Road, Hillsborough, NJ 08876 (US). (74) Agents: LICATA, Jane, Massey et al.; Law Offices of Jane Massey Licata, 66 E. Main Street, Marlton, NJ 08053 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NOVEL REDOX CLAMPING AGENTS AND USES THEREOF		
(57) Abstract <p>Redox clamping agents which maintain cells in a selected redox state are provided. Also provided are methods of using the redox clamping agents to sensitize cells to chemotherapeutic agents such as antineoplastics, to inhibit hyperproliferation of cells and to stabilize the redox state of cells with abnormal fluctuations in their redox state.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03878

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 39/395

US CL :424/130.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, WEST

search terms: cancer, butyrate, dimercaptosuccinic acid, merceptoethane-sulfonic acid, redox

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NEAL et al. Effects of N-acetylcysteine and 2,3-dimercaptosuccinic acid on lead induced oxidative stress in rat lenses. Toxicology. 1998, Vol. 130, pages 167-174. See entire document.	1, 5
X	BENARD et al. Modulation of glutathione level during butyrate-induced differentiation in human colon derived HT-29 cells. Molecular and Cellular Biochemistry. 1997, Vol. 170, pages 109-114. See entire document.	1, 5

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*&* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 JUNE 2000

Date of mailing of the international search report

06 JUL 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

MINH-TAM DAVIS

Telephone No. (703) 308-0916

JOYCE BRIDGERS
PARALEGAL SPECIALIST
CHEMICAL PATENT
JAB

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03878

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GLEAVE et al. Butyrate analogue, isobutyramide, inhibits tumor growth and time to androgen-independent progression in the human prostate LNCaP tumor model. J Cellular Biochemistry. 1998, Vol. 69 pages 271-281. See entire document	2-3